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54 **SUSPENDED-RELEASE PREPARATION PREPARED BY USING ALGINIC ACID.**

57 A suspended-release preparation containing a basic drug, which is readily prepared by using alginic acid gel beads as a suspended-release carrier and incorporating therein a basic drug such as a β -blocker or a calcium antagonist. This preparation is capable of releasing the basic drug contained therein at a desired rate by oral administration, etc.

EP 0 357 793 A1

TITLE

SPECIFICATION

SLOW-RELEASING PHARMACEUTICALS PREPARED WITH
ALGINIC ACID

5

[Field of the Invention]

This invention relates to a slow-releasing pharmaceutical in which a basic medicament is contained in alginic acid gel beads and to a method for the production of the same.

10

[Description of the Prior Art]

Recently, the preparations of slow-releasing pharmaceuticals have been designed for the purpose of improving effectiveness and safeness of medicaments since slow-releasing pharmaceuticals reduce number of doses, retain the expression of specified effects or reduce the incidence of side effects or toxicity as compared to ordinary fast-releasing pharmaceuticals.

20

Regarding these slow-releasing pharmaceuticals, in order to control the rate of release of medicaments in the body, various kinds of formulation of pharmaceuticals in forms such as microcapsules, nano-capsules and matrices using various natural polymers, synthetic polymers, synthetic elastomers or the like have been suggested.

25

For example, Shigeru Goto and Masakazu Kawada ("New

Pharmaceutical Development System General Technology Design" R&D Planning Company, p.140, 1986) disclosed preparation of microcapsules or nano-capsules. Furthermore, matrix preparations have been disclosed by M.

- 5 Bamba et al. (Int. J. Pharmaceut., 2307, 1979) and F. A. Kincl et al. (Archiv. Pharm., 317, 1984) and R. V. Sparer et al. (J. Contr. Release, 1, 23, 1984).

However, these preparations have problems such that the choice of combinations of medicaments and
10 polymers and that processes of the preparation of slow-releasing pharmaceuticals thereby are complex.

The present inventors found that a pharmaceutical having a sufficiently slow-releasing property can be obtained by such simple means that a basic medicament
15 is contained in alginic acid gel beads prepared with a polysaccharide, alginic acid which is a kind of natural polymer and a constituent of the cell membrane of brown algae.

Further, alginic acid is commercially available
20 in forms of sodium salts having various molecular weight. Since alginic acid is slowly dissolved in water and highly viscous, it is used as a stabilizer or viscous agent in viscous foods such as ice cream, cheese, sherbet and syrup and also used in manufacturing films
25 and fabrics.

[Disclosure of the Invention]

Objects of the present invention are to provide a pharmaceutical of a basic medicament having desirable slow-releasing properties using alginic acid gels, and to provide a method for the preparation of the same.

A slow-releasing pharmaceutical of the present invention is characterized by including a basic medicament in acidic alginic acid gel beads so as to form preferable binding features and to give preferable slow-releasing effects.

[Brief Description of the Drawings]

Fig. 1 shows the release of pindolol from the alginic acid gel beads in Example 1. Fig. 2 shows the change in the serum pindolol concentration after oral administration of the alginic acid gel beads to rabbits. Fig. 3 shows the change in the serum pindolol concentration after oral administration of the alginic acid gel beads to beagle dogs. Fig. 4 shows the absorption of pindolol in the alginic acid gel beads in beagle dogs.

Fig. 5 shows release of nifedipine from the alginic acid gel beads in Example 2. Fig. 6 shows the absorption of nifedipine contained in alginic acid gel beads.

Furthermore, Fig. 7 shows the releasing effect of alginic acid gel beads with the M/G ratio of 1:3 as compared to alginic acid gel beads with other M/G ratios. Fig. 8 shows the change of the serum pindolol concentration in beagle dogs orally administered with pindolol powder and with alginic acid gel beads with the same M/G ratio as above.

[Best Mode of Carrying Out the Invention]

Examples of the basic medicaments to be used in the present invention include beta-blocking agents such as pindolol, procaterol, propranolol, pytelol, and befunolol; calcium antagonists such as nifedipine, verapamil, diltiazem, and nicardipine; antihistamine agents such as difenhydramine, diphenylpyraline and chlorophenylamine; diuretics such as triamterene and penflutizide, vasodilative agents such as cinnarizine, ifenprodil, and pentoxifylline; and antitussives such as eprazinone, chloroprenaline, chloperastine, trimethoquinol, bromhexine, methoxyphenamine and sulbutanol.

In the present invention, alginic acid gel containing the above basic medicaments can be prepared using commercially available sodium alginates. However, in order to accomplish continuous and appropriate release of medicaments, particularly, sodium alginates

having a molecular weight of about 10,000 - 100,000 are preferably used. 1% solutions of such sodium alginates have a viscosities of less than 100 cps and are useful in designing a preferable releasing system by selecting suitable sodium alginate depending on the kinds of medicament and releasing patterns.

In the present invention, alginates having the following features were used.

	Sodium alginate	MM/GG	Viscosity (cp)
10	No. 1	0.13	13.3
	No. 2	0.66	13.7
	No. 3	1.77	12.1

Consequently, as for the alginic acid gel, it has been revealed that the release of the above-mentioned medicaments are affected by the difference in the ratio (M/G ratio) of constituent sugars of the alginic acid, i.e. mannouronic acid (M) and guluronic acid (G). Further, it has also been revealed that the above-mentioned release is affected by the ratio of homo-block (MM) of mannuronic acid (M) and homo-block (GG) of guluronic acid (G) and furthermore the viscosity of alginic acid. Herein, the homo-block (MM, GG) means a block in which the same uranic acid (M or G) is sequenced.

In other words, when the amount of guluronic

acid in the sugar composition increases, the matrix becomes so dense that the release of a medicament in the alginic acid gel beads becomes difficult. Also, when the MM/GG ratio is small, for example 0.13, the
5 medicament can be released slowly.

According to the present invention, alginic acid gel beads which contain a basic medicament can be prepared as follows:

A basic medicament is suspended in a 4%
10 sodium alginate solution and added drop by drop through a nozzle to a 0.1 M CaCl_2 solution. The solution is allowed to stand for 72 hours and then alginic acid gel beads containing the basic medicament are collected by filtration. The alginic acid gel beads
15 are dried in air for 24 hours and then dried in vacuo at room temperature for 24 hours.

In the above process, the molecular weight of the sodium alginate greatly affects both the yield of alginic acid gel beads formed and the content of the
20 medicament contained in the alginic acid gel beads. With a view to controlling the release, alginic acid having a low viscosity, i.e. a low molecular weight, is preferably used.

Prior to preparation, the concentration of the
25 basic medicament should be determined by considering the amount necessary to achieve the desired release.

According to the present invention, the alginic acid gel beads containing a basic medicament, thus obtained, can be formulated as necessary, for example, into enteric coated pills.

5 Further, a pharmaceutical according to the present invention can be expected to control the absorption of sodium in the body, since alginic acid forms gel structures by binding to calcium and thus calcium is replaced by sodium when the alginic acid
10 is diffused to release the medicament therefrom in the intestine.

A process for the preparation of the slow-releasing pharmaceutical of the present invention and releasing effects of the same are explained more in
15 detail by the following Examples.

Example 1

Preparation of alginic acid gel beads:

As a basic medicament, a beta-blocking agent,
20 pindolol, was suspended in a 4% sodium alginate solution (M/G ratio of alginic acid = 0.6) to make a pindolol concentration to 4% and the resultant suspension was added drop by drop using a nozzle into a 0.1 M CaCl_2 solution. The resultant mixture was allowed to stand
25 for 72 hours so as to prepare alginic acid gel beads containing pindolol therein.

The gel beads thus obtained were collected by filtration, dried in air for 24 hours and then dried in vacuo for 24 hours at room temperature. The resultant preparation was subjected to a medicament releasing test, oral administration tests in rabbits or beagle dogs and an absorption test of the medicament in humans.

The sodium alginates used were as follows:

- (1) A product of Kimizu Chemicals, sodium alginate with low viscosity (IL₂), the viscosity of a 1% solution:
20 - 50 cps;
- (2) A product of Kimizu Chemicals, sodium alginate of ultra low viscosity (ULA), the viscosity (10% solution):
500 cps;
- (3) A product of Wako Pure Chemicals, reagent grade sodium alginate (NA), the viscosity (1%): 20 cps; and
- (4) A product of Kibun Food Chemipha, Dack alginic acid (DA-20), the viscosity (1%): 20 cps.

Further, the pindolol content and yield in alginic acid gel beads are shown in Table 1.

20

Table 1

	Pindolol (%)	Recovery (%)
NA	47.2	78.9
IL ₂	44.9	75.8
25 ULA	14.5	21.5
DA-20	60.2	77.5

Medicament releasing test:

Alginic acid gel beads containing 10 mg of pindolol as pindolol were suspended in 150 ml of water maintained at 37°C. The suspension was stirred at 150 rpm and the medicament released was measured at given intervals.

As shown in Fig. 1, the rate of the release of pindolol was much slower from the alginic acid gel beads than from pindolol by itself. Furthermore, the lower the viscosity of sodium alginate used (i.e., the smaller the degree of polymerization of alginic acid), the better was the release of pindolol.

Oral administration test in rabbits:

Male Japanese white rabbits (2.0 - 2.5 kg) were starved for 24 hours before the administration of medicaments.

alginic acid gel beads (30 mg/kg as pindolol) was administered with 10 ml of the alginic acid gel beads to the test animals and 3 ml of blood sample was taken from the auricular veins of each animals at given intervals. The samples were centrifuged and 1 ml each of serum was obtained. Pindolol was extracted from the serum and was quantitatively measured by high performance liquid chromatography (HPLC).

As shown in Fig. 2, the pindolol concentration transferred to the serum after the oral administration

to the rabbits was lower in the case of administration of pindolol as alginic acid gel beads than as pindolol by itself. As evident from the results, pindolol contained in the alginic acid gel beads was absorbed slowly, which showed slow-releasing effects. Moreover, the higher the viscosity of alginic acid, the smaller were the rate and amount of pindolol absorption. Consequently, it is considered that the pindolol concentration in the serum can be controlled by the combination of various kinds of alginic acid gel beads. Oral administration test using beagle dogs:

Male beagle dogs (10 kg) were starved for 24 hours before the administration of a test medicament. Water was given ad libitum.

In the case of the administration of pindolol by itself, a total amount 5 mg/kg of a powdered medicament was administered, i.e. 2.5 mg/kg with 20 ml of water at the start and 6 hours later. In the case of the administration of pindolol contained in alginic acid gel beads, 5 mg/kg was orally administered with 20 ml of water. Water was given ad libitum during the test period. At given intervals, 5 ml of blood was taken from the forefoot vein and centrifuged so as to obtain 2 ml each of the serum. The medicament was extracted from the serum and quantitatively determined by high performance liquid chromatography (HPLC).

In this test, alginic acid gel beads prepared using the low viscosity alginic acid gel beads (IL₂, Kimizu Chemicals) were used.

Results are shown in Fig. 3.

5 Further, the results of the velocity analysis of the concentration of the medicament in the serum are shown in Table 2.

Table 2

10	Form of preparation and time elapsed	AUC (ngh/ml)	MRT (h)	VRT (h ²)
	Pindolol powder			
	0 → 6h	238.0	1.74	1.74
	0 → 12h	311.4	1.98	1.83
	Alginic acid gel beads			
15	0 → 12h	445.7	4.62	5.93

AUC: Concentration in the serum - Area under the time curve

MRT: Mean retention time (average time in which the
20 medicament retain in the body; the faster the absorption, the smaller the value of MRT.)

VRT: Variance of retention time (the longer the retention, the larger the value of VRT).

25 The results of this analysis revealed that pindolol contained in the alginic acid gel beads was

absorbed more slowly and moreover retained activity longer than pindolol by itself. Namely, the slow-releasing effect by the use of alginic acid gel beads was observed.

Absorption test in humans:

5 The alginic acid gel beads (alginic acid having $MM/GG = 0.66$ was used) that was revealed to be the most advantageous slow-releasing pharmaceutical in the oral administration test mentioned above were orally administered to four healthy human adults and compared with
10 a commercially available pindolol slow-releasing pharmaceutical, Calvisken (registered trademark, Sankyo Co., Ltd.). Calvisken is a release-retaining nucleated double-layered tablet in which 10 mg each of pindolol is contained in the core tablet and in the outer layer
15 and the enteric coat is coated on the core tablet.

Fig. 4 shows the change of pindolol concentration in the serum (figures are the average \pm standard deviation for the 4 adults). In the case where powdery pindolol was orally administered in an amount of half
20 (10 mg) of the slow-releasing pharmaceutical, T_{max} (time to reach the maximum serum concentration) was about 1 hour and the medicament in the serum was thereafter gradually disappeared. On the other hand, in the case of the two kinds of the slow-releasing
25 pharmaceuticals, for 1 to 6 hours after the administration, the pindolol concentration in the serum was

maintained comprative to C_{\max} (maximum serum concentra-
 tion) after the administration of powdery pindolol;
 thus it was confirmed that the alginic acid gel beads
 was biologically equivalent to calvisken R. Since
 5 the effective concentration of pindolol in the serum
 is 10 - 50 ng/ml, in the case of the alginic acid gel
 beads, the serum pindolol concentration is rather
 exceedingly high for 3 hours after the administration.
 However, the effective pindolol concentration in the
 10 serum was maintained for 10 hours after the administra-
 tion. Velocity parameters obtained by the analysis of
 the change in the concentration in the serum are shown
 in Table 3.

Table 3

Form of preparation	AUC (ng h/ml)	MRT (h)	VRT (h ²)
Pindolol powder	377.5±48.5*	3.82±0.32	7.44±0.54
Alginic acid gel beads	336.3±43.3**	4.66±0.42 ^{a)}	8.16±0.47
20 Calvisken R	305.7±25.7**	5.07±0.30 ^{a)}	7.49±0.37

Note: * $AUC_{0-6} \times 2$ ** AUC_{0-12}

a) $p < 0.05$ to the value for powdery pindolol

(Significantly different from that for powdery pindolol
 25 at the significance level of 5%)

As shown in Table 3, the AUCs after the

administration of the slow-releasing pharmaceuticals were slightly smaller than the 2-fold of the AUC after the administration of powdery pindolol; but significant difference was not observed. Furthermore, the MRT for
5 the slow-releasing pharmaceuticals is longer than that for the powdery pindolol; thus, the slow releasing effect was confirmed.

Consequently, it was clear that the alginic acid gel beads prepared according to this example
10 were as effective as the commercially available slow-releasing tablet, Calvisken R; thus the usefulness of the alginic acid as a slow-releasing carrier was confirmed.

15 Example 2

Preparation of alginic acid gel beads:

As a basic medicament, a calcium antagonist, nifedipine, was suspended in a 4% low viscosity sodium alginate solution (IL₂, KimiTM Chemicals) to make
20 a pindolol concentration to 4% and then the suspension was added drop by drop using a nozzle into a 0.1 M CaCl₂ solution. The resultant mixture was allowed to stand for 72 hours so as to prepare alginic acid gel beads containing nifedipine.

25 The content of nifedipine in the gel beads thus obtained was 45%.

The gel beads were collected by filtration, dried in air for 24 hours and then dried in vacuo for 24 hours at room temperature. The resultant preparation was subjected to the medicament releasing test.

5 Medicament releasing test:

The alginic acid gel beads corresponding to 10 mg as nifedipine were suspended in 150 ml of water maintained at 37°C. The suspension was stirred at 150 rpm and the medicament released was measured at given
10 intervals.

As shown in Fig. 5, the rate of the release of nifedipine was much slower from the alginic acid gel beads than from nifedipine by itself.

Absorption test in beagle dogs:

15 The oral administration to beagle dogs was carried out in the same manner as described in Example 1 using pindolol. The nifedipine concentration in the serum was determined in the same manner as described in Example 1.

20 As shown in Fig. 6, nifedipine contained in the alginic acid gel beads was absorbed more slowly and more extensively than pindolol in powder form.

Example 3

25 This example is carried out to demonstrate the effect of the ratio of mannuronic acid and guluronic

acid (M/G ratio) in the constituent sugar in alginic acid used for alginic acid gel beads on the slow releasing effect of a medicament.

Preparation of alginic acid gel beads:

5 Sodium alginates having the M/G ratios of 0.5, 1.3 and 2.4 were used. Alginic acid gel beads were individually prepared in the same manner as described in Example 1.

10 Then, the alginic acid gel beads thus obtained were subjected to the medicament releasing test according to the procedure described in Example 1 to investigate the releasing pattern of pindolol. As shown in Fig. 7, it was revealed that at the M/G ratio = 1.3, the rate of the release of pindolol was appro-
15 priately controlled. Moreover, the oral administration test using beagle dogs was carried out in the same manner as in Example 1 so as to investigate the change in the concentration of pindolol in the serum. Results are shown in Fig. 8. As shown in Fig. 8, the advantage of the use
20 of the alginic acid gel beads prepared using alginic acid having the M/G ratio = 1.3 was observed.

[Possible Industrial Use]

25 A slow-releasing pharmaceutical of the present invention can be prepared containing a basic medicament in alginic acid gel beads, in which the M/G ratio,

MM/GG ratio and the molecular weight of the alginic acid to be used are selected depending on the desired releasing rates and, furthermore, alginic acid gel beads having an appropriate matrix structure are
5 easily prepared using a metal ion such as Ca ion or the like for the alginic acid gel formation. As a result, a pharmaceutical which exerts the desirable effect of slow-releasing of effective ingredients can be prepared.

Furthermore, since the pharmaceutical of the
10 present invention exerts the slow-releasing effect also by ordinary oral administration, it is extensively applicable in the field of medicine. In particular, it is extremely useful in the field where retention of the effect of efficacious ingredients and reduction in the
15 number of dose are desirable or in the field where manifestation of side effects or toxicity due to prompt effectiveness is apprehended.

Furthermore, the slow releasing pharmaceutical prepared with the alginic acid gel beads according to
20 the present invention is extensively applicable in various kinds of chemical reactions as a catalyst or additive. Furthermore, the alginic acid gel beads are widely applicable to a fertilzier, agricultural chemical, soil chemicals, food additive or the like
25 because the gel beads can be easily formulated into various forms.

Claims

- (1) A slow-releasing pharmaceutical characterized in that a basic medicament is contained in alginic acid gel beads.
- 5 (2) The slow-releasing pharmaceutical as set forth in claim (1), wherein said basic medicament is a beta-blocking agent.
- 10 (3) The slow-releasing pharmaceutical as set forth in claim (2), wherein said beta-blocking agent is pindolol.
- (4) The slow-releasing pharmaceutical as set forth in claim (1), wherein said basic medicament is a calcium
15 antagonistic agent.
- (5) The slow-releasing pharmaceutical as set forth in claim (4), wherein said calcium antagonistic agent is nifedipine.
- 20 (6) A process for the production of a slow-releasing pharmaceutical, which comprises suspending a basic medicament in a sodium alginate solution, adding drop by drop the resultant suspension through a nozzle to a
25 calcium chloride solution, allowing to stand the mixture, drying the alginic acid gel beads thus formed and thereby

containing the basic medicament in the alginic acid gel beads.

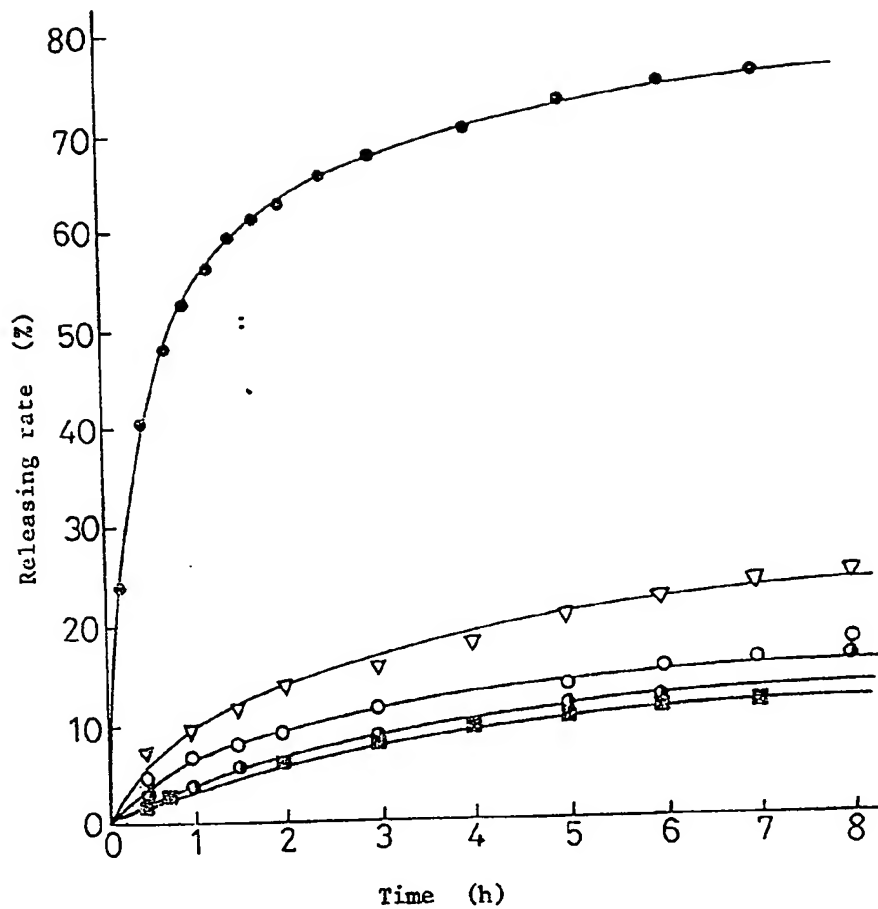
(7) The process as set forth in claim (6) for the
5 production of a slow-releasing pharmaceutical, in which
said solution of the basic medicament is a 4% pindolol
solution.

(8) The process as set forth in claim (6) for the
10 production of a slow-releasing pharmaceutical, in which
said solution of the basic medicament is a 4% nifedipine
solution.

(9) The process as set forth in claim (6) for the
15 production of a slow-releasing pharmaceutical, in which
said suspension is added drop by drop through a nozzle to
a calcium chloride solution and then allowed to stand
for about 72 hours.

FIG. 1

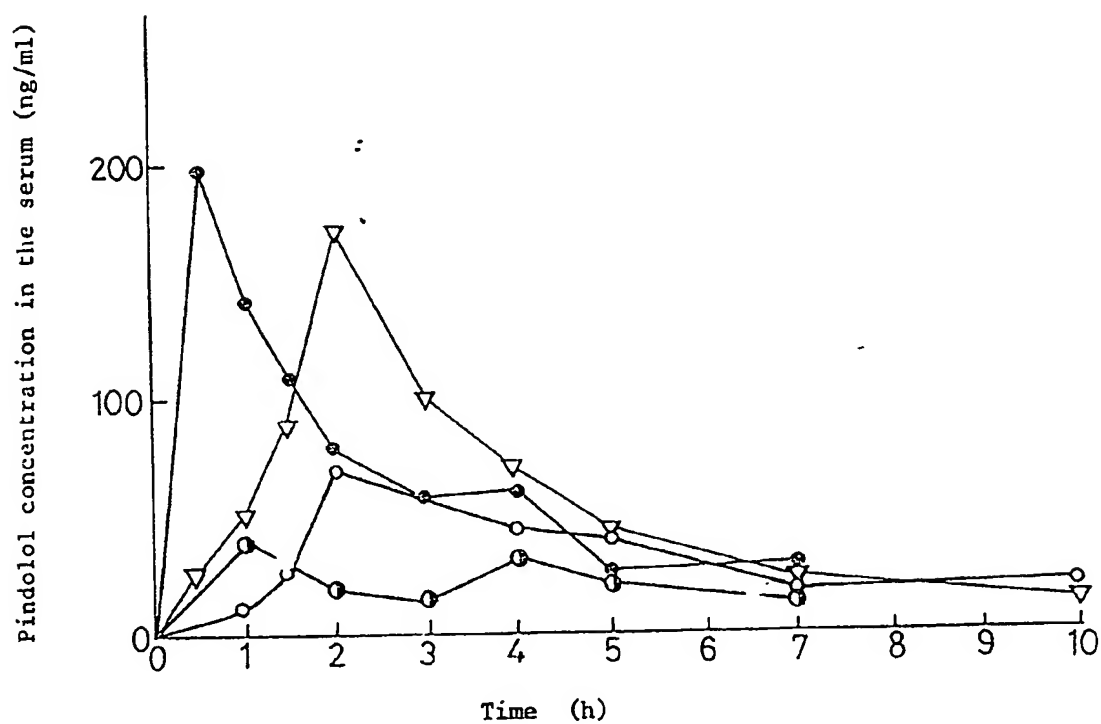
Release of pindolol from alginic acid gel beads



- : Pindolol administered in powder form
- ▽ : Pindolol administered in ULA alginic acid gel beads
- : Pindolol administered in IL₂ alginic acid gel beads
- ◐ : Pindolol administered in NA alginic acid gel beads
- ◑ : Pindolol administered in DA-20 alginic acid gel beads

FIG. 2

Change in the concentration of pindolol in the serum of rabbits that are orally administered with pindolol in powder form or pindolol contained in alginic acid gel beads.



- : Pindolol administered in powder form
- ▽ : Pindolol administered in ULA alginic acid gel beads
- : Pindolol administered in IL₂ alginic acid gel beads
- ⊙ : Pindolol administered in NA alginic acid gel beads

FIG. 3

Change in the concentration of pindolol in the serum of beagle dogs that are orally administered with pindolol in powder form or pindolol contained in alginic acid gel beads

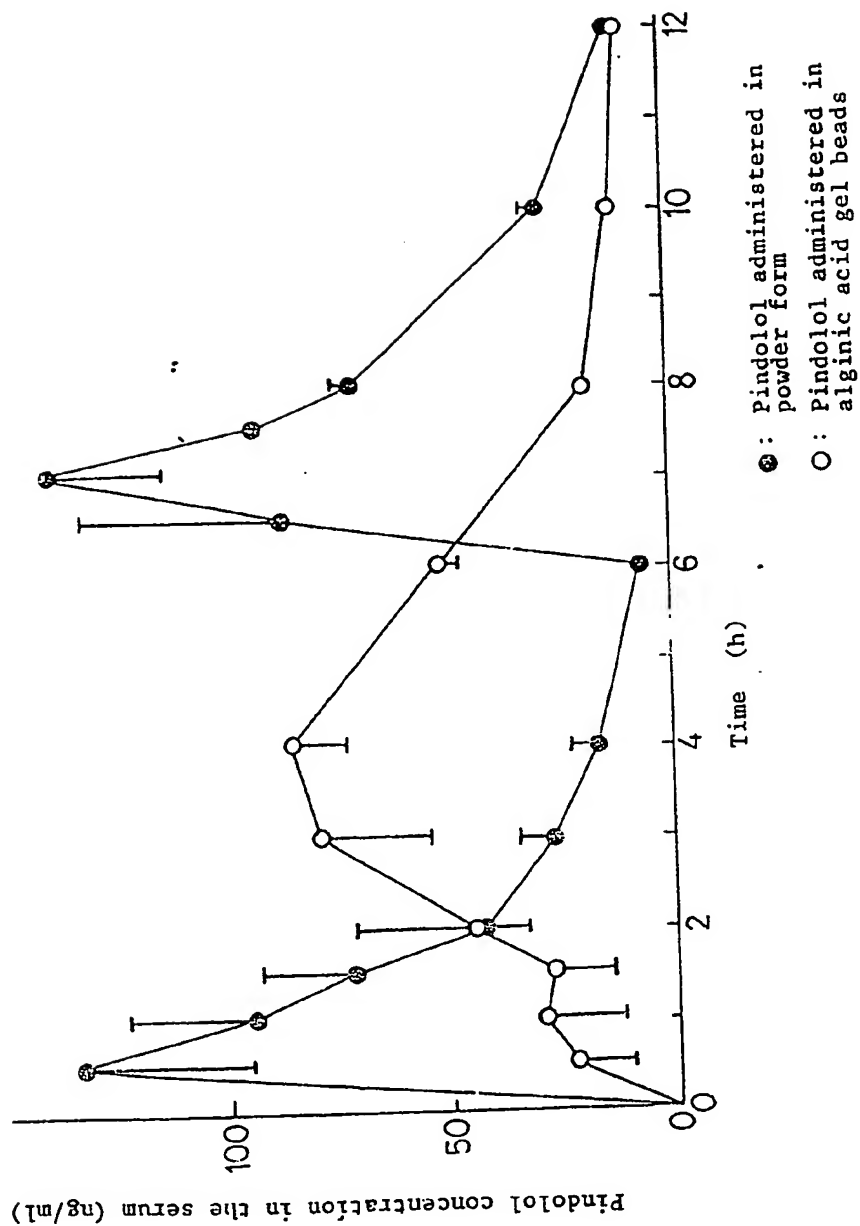
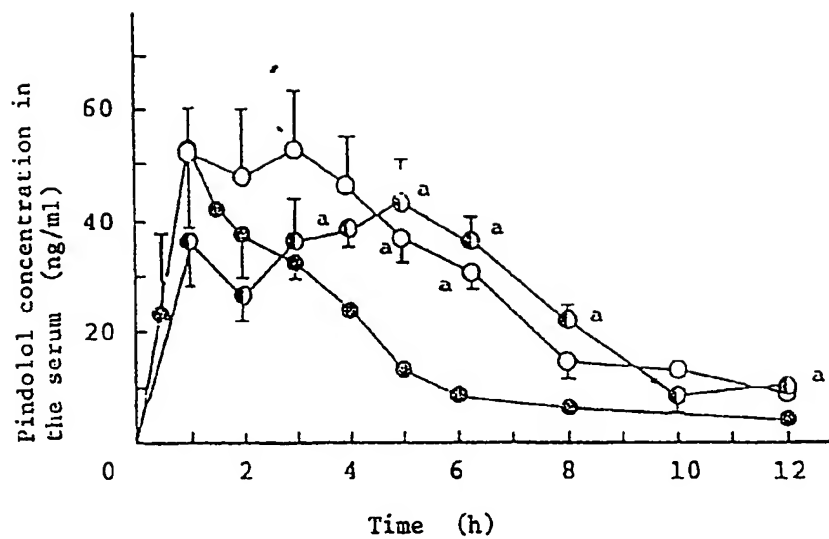


FIG. 4



● : Pindolol administered in powder form

○ : Pindolol administered in alginate acid gel beads

◐ : Pindolol administered in Calvisken R

a : $P < 0.05$ to powdered pindolol

Release of nifedipine from powdered nifedipine and
alginic acid gel beads containing nifedipine

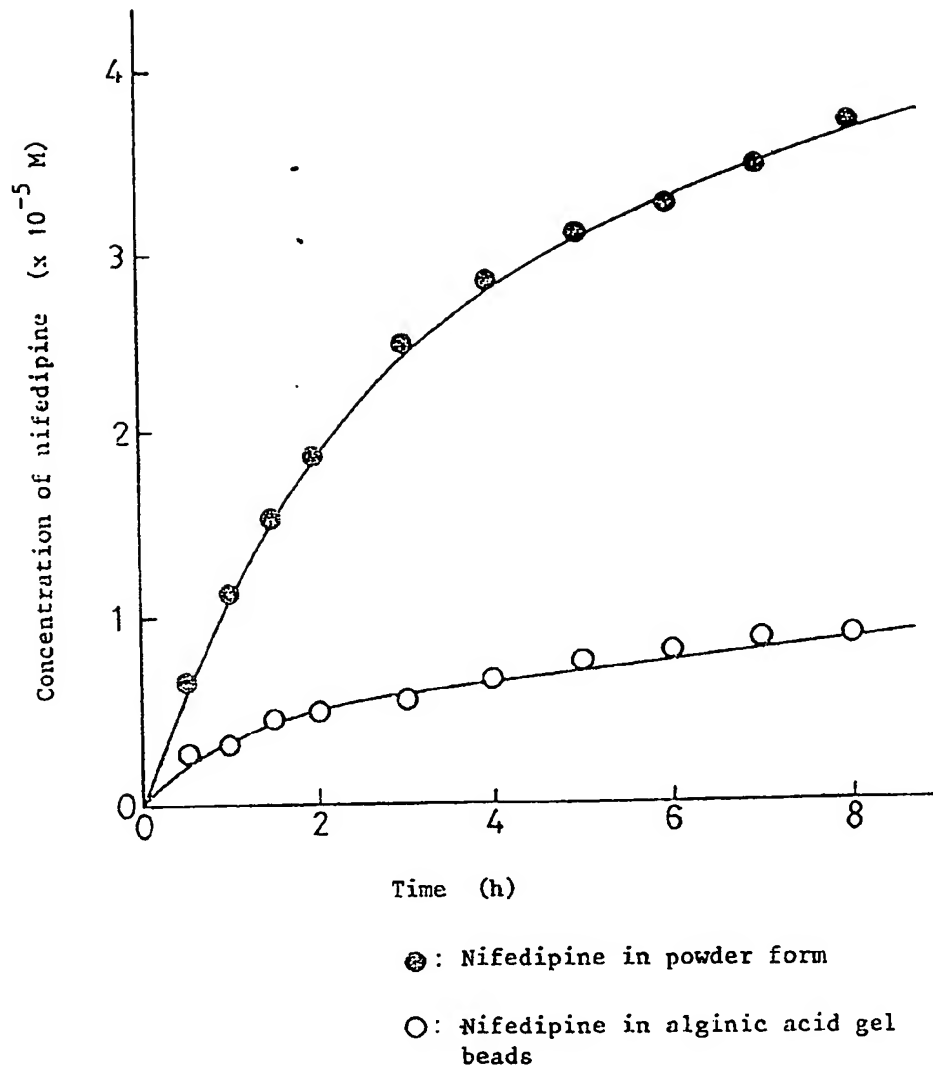
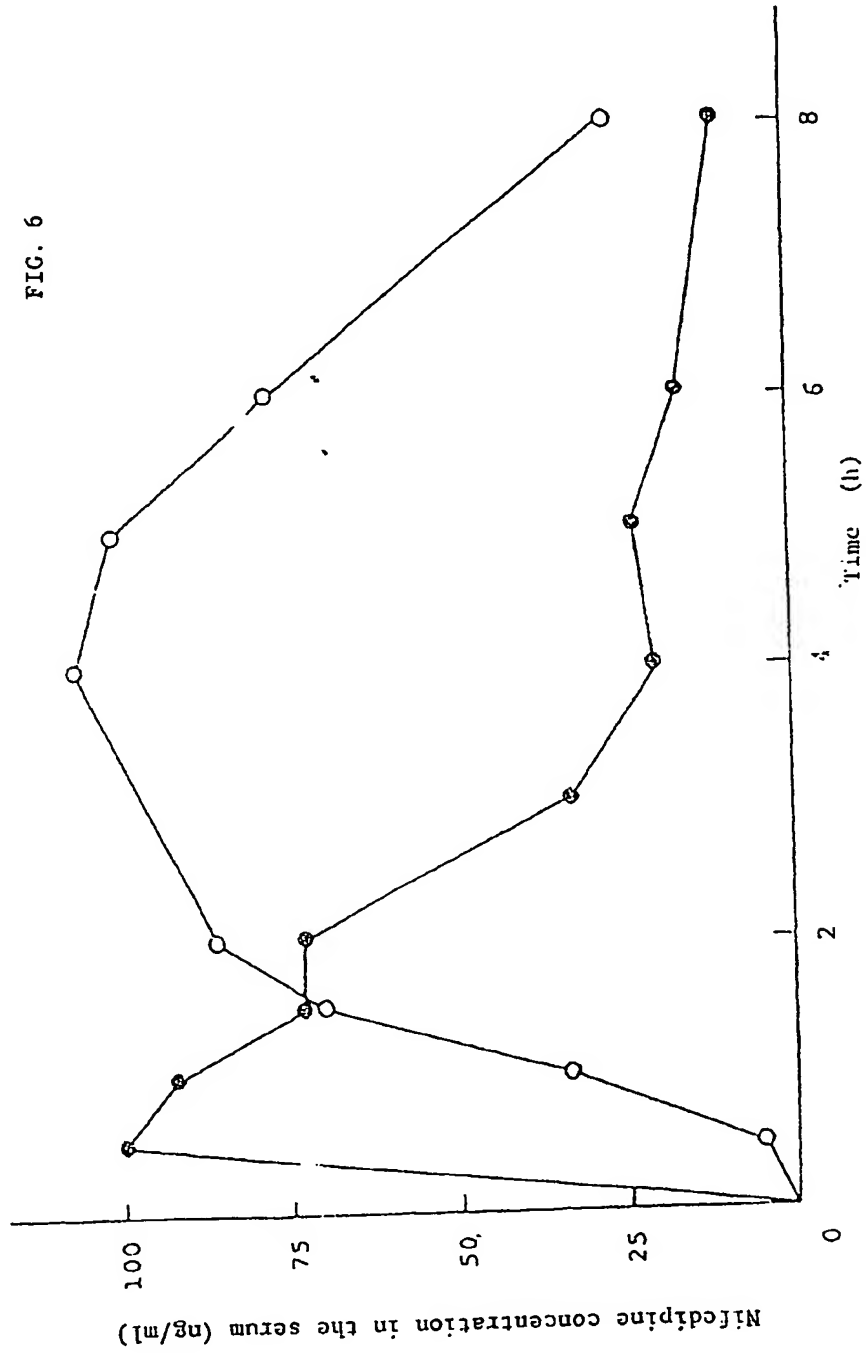


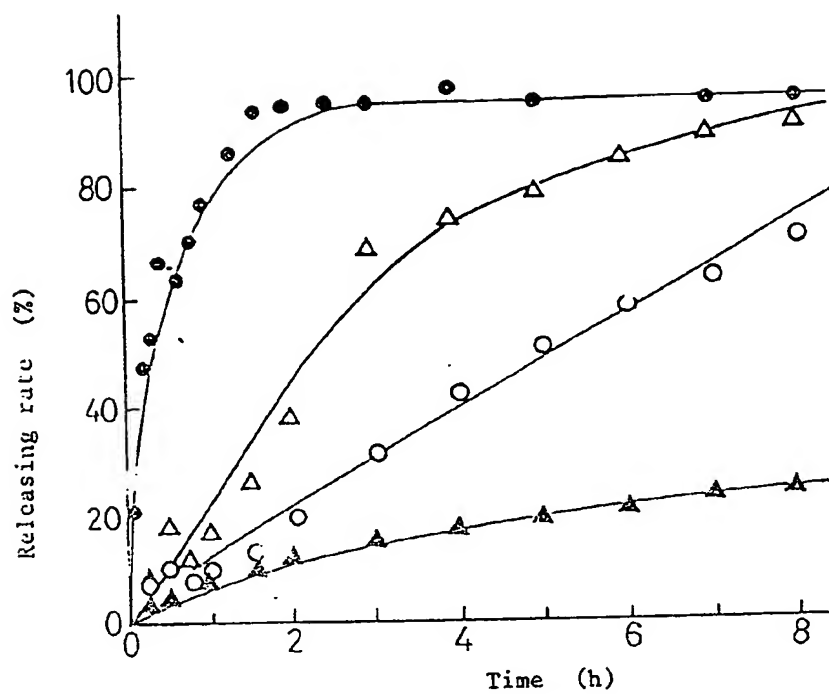
FIG. 6



Change in the concentration of nifedipine in the serum after oral administration of nifedipine in powder form or nifedipine contained in alginate acid gel beads

● : Powder form ○ : Gel beads

FIG. 7



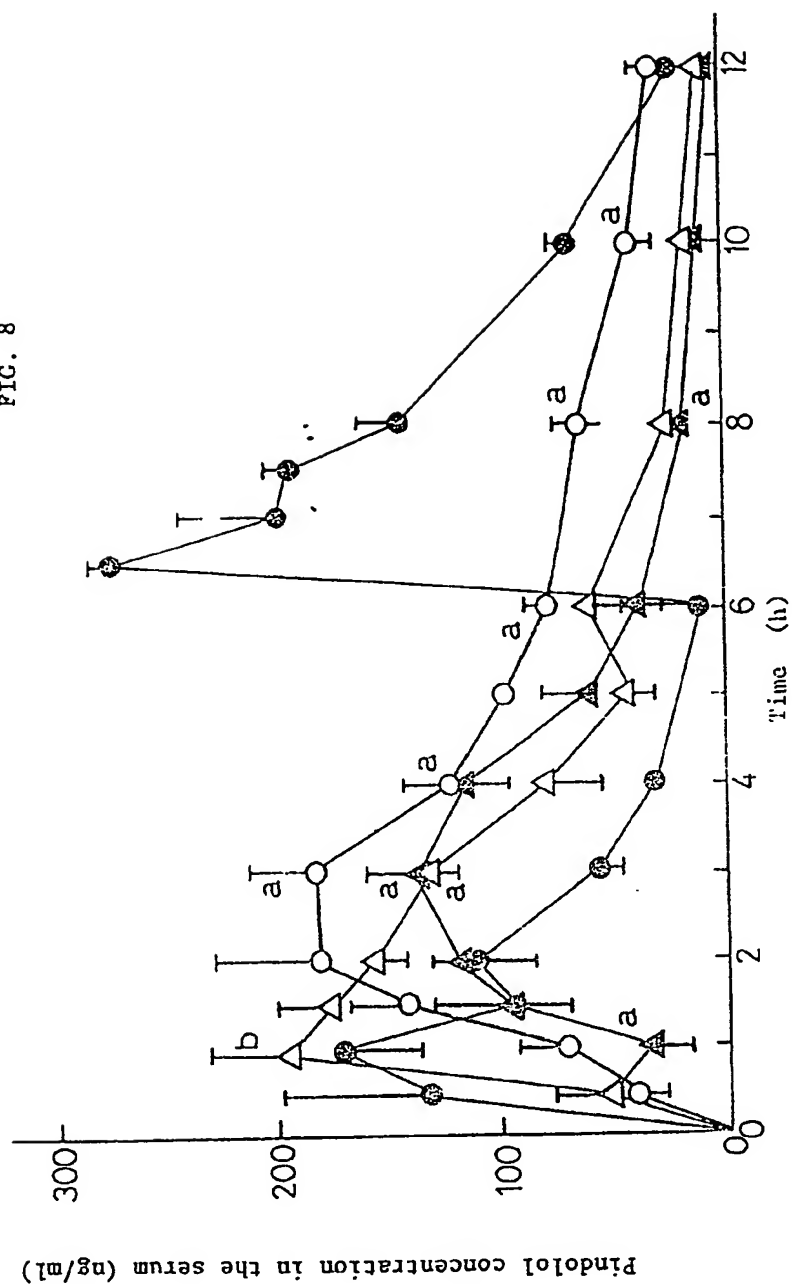
● : Pindolol in powder form

▲ : Pindolol in alginate acid gel beads
M/C ratio = 0.53

○ : Pindolol in alginate acid gel beads
M/C ratio = 1.3

△ : Pindolol in alginate acid gel beads
M/C ratio = 2.4

FIG. 8



INTERNATIONAL SEARCH REPORT

International Application No PCT/JP89/00255

I. CLASSIFICATION OF SUBJECT MATTER (If several classification symbols apply, indicate all) ⁴ According to International Patent Classification (IPC) or to both National Classification and IPC <div style="text-align: center; padding: 10px;"> Int. Cl⁴ A61K9/16, A61K9/62, A61K47/00 </div>								
II. FIELDS SEARCHED <div style="text-align: center; padding: 5px;">Minimum Documentation Searched ⁷</div> <table style="width: 100%; border: none;"> <tr> <td style="width: 50%; border: none;">Classification System :</td> <td style="width: 50%; border: none;">Classification Symbols</td> </tr> <tr> <td style="border: none; padding: 10px;">IPC</td> <td style="border: none; padding: 10px;">A61K9/16, 9/50-9/62, 47/00</td> </tr> </table> <div style="text-align: center; padding: 5px;">Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched ⁷</div>			Classification System :	Classification Symbols	IPC	A61K9/16, 9/50-9/62, 47/00		
Classification System :	Classification Symbols							
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III. DOCUMENTS CONSIDERED TO BE RELEVANT ⁵ <table style="width: 100%; border: none;"> <tr> <td style="width: 10%; border: none;">Category ⁶</td> <td style="width: 60%; border: none;">Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²</td> <td style="width: 30%; border: none;">Relevant to Claim No. ¹³</td> </tr> <tr> <td style="border: none; vertical-align: top; padding: 10px;">X</td> <td style="border: none; vertical-align: top; padding: 10px;">JP, A, 61-44823 (Connaught Laboratories Ltd.) 4 March 1986 (04. 03. 86) Page 9, lower right column, page 10, upper left column & EP, A, 167690</td> <td style="border: none; vertical-align: top; text-align: center; padding: 10px;">1-9</td> </tr> </table>			Category ⁶	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³	X	JP, A, 61-44823 (Connaught Laboratories Ltd.) 4 March 1986 (04. 03. 86) Page 9, lower right column, page 10, upper left column & EP, A, 167690	1-9
Category ⁶	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³						
X	JP, A, 61-44823 (Connaught Laboratories Ltd.) 4 March 1986 (04. 03. 86) Page 9, lower right column, page 10, upper left column & EP, A, 167690	1-9						
<table style="width: 100%; border: none;"> <tr> <td style="width: 50%; border: none; vertical-align: top;"> ⁸ Special categories of cited documents: "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier document but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed </td> <td style="width: 50%; border: none; vertical-align: top;"> "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "Δ" document member of the same patent family </td> </tr> </table>			⁸ Special categories of cited documents: "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier document but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "Δ" document member of the same patent family				
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IV. CERTIFICATION <table style="width: 100%; border: none;"> <tr> <td style="width: 50%; border: none; padding: 5px;"> Date of the Actual Completion of the International Search <div style="text-align: center; padding: 5px;">May 12, 1989 (12. 05. 89)</div> </td> <td style="width: 50%; border: none; padding: 5px;"> Date of Mailing of this International Search Report <div style="text-align: center; padding: 5px;">May 29, 1989 (29. 05. 89)</div> </td> </tr> <tr> <td style="width: 50%; border: none; padding: 5px;"> International Searching Authority <div style="text-align: center; padding: 5px;">Japanese Patent Office</div> </td> <td style="width: 50%; border: none; padding: 5px;"> Signature of Authorized Officer </td> </tr> </table>			Date of the Actual Completion of the International Search <div style="text-align: center; padding: 5px;">May 12, 1989 (12. 05. 89)</div>	Date of Mailing of this International Search Report <div style="text-align: center; padding: 5px;">May 29, 1989 (29. 05. 89)</div>	International Searching Authority <div style="text-align: center; padding: 5px;">Japanese Patent Office</div>	Signature of Authorized Officer		
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